DaTSCAN™ (Ioflupane I 123 Injection)

Briefing Document

Peripheral and Central Nervous System Advisory Committee Meeting

August 11, 2009

GE Healthcare

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1 EXECUTIVE OVERVIEW

1.1 Introduction

GE Healthcare is seeking approval of DaTSCAN™ (Ioflupane I 123 Injection) in the United States, as a single-dose, intravenously administered imaging agent to visually detect loss of functional nigrostriatal dopaminergic neurons, defined in this document as a striatal dopaminergic deficit (SDD). DaTSCAN was approved in Europe in 2000 and is now approved in 32 countries. Over 216,000 patients have been safely exposed to DaTSCAN up to June 17, 2009 via clinical studies and the marketplace.

A New Drug Application for DaTSCAN is undergoing review by the U.S. Food and Drug Administration and has been assigned a "Priority Review" classification, as the product meets an unmet medical need. The DaTSCAN application will be discussed at the Peripheral and Central Nervous System Advisory Committee Meeting on August 11, 2009. The proposed indication for DaTSCAN in the United States is:

> *"DaTSCAN is a radiopharmaceutical containing [^{123}I]ioflupane, indicated for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration."*

The active component of DaTSCAN is ioflupane, labeled with the radioactive isotope, iodine-123, which releases gamma radiation suitable for medical imaging.

Following a single intravenous administration, ioflupane binds with high affinity to the dopamine transporter (DaT) protein. The DaT protein is located in the striata in the brain, on the axons of nigrostriatal neurons near the synapses. Its function is to facilitate re-uptake of dopamine into the nigrostriatal neurons to terminate cell signaling and to allow recycling of dopamine. This protein is specific to dopaminergic neurons, which are found predominantly in the nigrostriatal pathway.

By binding to the DaT protein, ioflupane allows imaging of nigrostriatal neurons, producing images of the striata which appear as symmetric crescent-shaped areas of brightness on a darker background (Figure 1, left).

Loss of nigrostriatal neurons results in loss of DaT protein, which results in the striatal defects visible on DaTSCAN images: abnormal striata are smaller or absent on DaTSCAN images (Figure 1, right).

Because extensive loss of nigrostriatal neurons occurs before symptom onset, DaTSCAN images from symptomatic patients are easily recognized and quantitative image analysis is therefore not needed. Visual assessment of DaTSCAN images has high sensitivity and specificity in detecting loss of DaT protein binding capacity, indicative of loss of nigrostriatal neurons. Image interpretation has > 90% inter- and intra-reader reproducibility.

The abnormal image patterns produced in patients with parkinsonian syndromes and dementia with Lewy bodies are usually similar; therefore, DaTSCAN images alone do not allow identification of the specific disease associated with a neuronal loss. However, the addition of DaTSCAN image findings to other clinical information may enable a more accurate diagnosis.

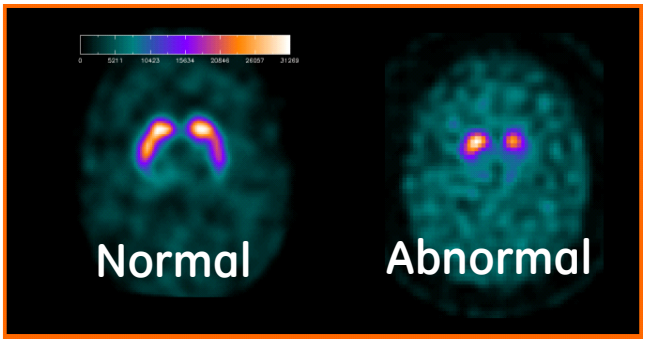

Figure 1 Examples of DaTSCAN images

1.2 Medical Need/Rationale

Medical Need

Loss of nigrostriatal neurons results in parkinsonian signs such as tremor, rigidity, bradykinesia, and gait disturbance. However, this is not the only cause of parkinsonism or its signs, both of which are common among persons aged 65 and older. The definitive diagnosis or exclusion of a parkinsonian disorder requires histologic examination of the brain, which is impractically invasive during life. Therefore, diagnosis in the United States currently depends on clinical signs and symptoms, but clinicopathologic studies have shown that this is frequently inaccurate.

The consequences of misdiagnosis can be significant. A false positive diagnosis of dopamine deficient parkinsonian syndrome may result in patients receiving dopaminergic drugs unnecessarily, with a potential for harm from adverse reactions. The diagnosis or exclusion of dementia with Lewy bodies is especially important because treatment of hallucinations and other psychotic symptoms with neuroleptic drugs may be dangerous in these patients.

Based on the above, there is a medical need for an earlier, more accurate, and more reproducible diagnosis of parkinsonian movement disorders and dementia. A non-invasive test to determine whether or not a patient has likely lost nigrostriatal neurons would be a helpful addition to clinical diagnosis. DaTSCAN could assist in meeting these medical needs.

Rationale for the Development of DaTSCAN

Autopsy studies have established that there is an SDD in some degenerative movement disorders and one form of dementia, but not in others that are in the differential diagnosis.

The loss of dopaminergic neurons is paralleled by loss of striatal dopamine. This finding is the rationale for current therapies with L-DOPA or dopamine receptor agonists. On the other

hand, an SDD is not seen with other diseases that may have similar symptoms such as Alzheimer's disease and essential tremor.

Dopaminergic neurons employ the DaT protein to assist in termination of neuron firing. This protein is specific to dopaminergic neurons found predominantly in the nigrostriatal pathway. Loss of nigrostriatal neurons results in loss of DaT protein.

The DaT protein is the site of binding of the drug cocaine, and analogs of cocaine that are radiolabelled to allow imaging have been prepared. The active component of DaTSCAN, [^{123}I]ioflupane, is a cocaine analog intended for use in imaging the DaT protein of nigrostriatal neurons. The doses of ioflupane needed for imaging are too small to have cocaine-like effects or abuse potential.

Loss of nigrostriatal neurons results in loss of the DaT protein, with consequent loss of DaT binding capacity for ioflupane. This is depicted on DaTSCAN images as reduced area of signal compared to images from healthy controls.

1.3 Clinical Development Program

An ongoing investigator-initiated study has demonstrated that a baseline DaTSCAN image correlates extremely well with the pathological status of a number of dementia and non-dementia patients at autopsy, hence validating the claim that DaTSCAN is able to detect a loss of functional nigrostriatal dopaminergic neurons.

Results from three GE-sponsored Phase 3 clinical studies (two with movement disorder patients and one with dementia patients) demonstrate that DaTSCAN accurately detects an SDD *in vivo*. Using expert clinical diagnosis as the standard of truth, these studies showed that DaTSCAN can routinely differentiate those patients who clearly do or do not have an SDD. As the deficit and DaTSCAN images are similar in both parkinsonian syndromes and dementia with Lewy bodies, the clinical data from these principal studies were pooled to give an estimate of the overall ability of DaTSCAN to detect an SDD.

Results of a post-marketing study in clinically uncertain parkinsonian subjects show that DaTSCAN image findings can significantly impact patient management such as initiating new therapeutic treatment or withdrawal of ongoing medication.

The safety of DaTSCAN imaging has been demonstrated in over 1,000 subjects in clinical studies. Radiation exposure is well below the threshold for concern.

1.4 Benefits and Risks in Patients with Suspected Movement Disorders and/or Dementia

Detection of an SDD with DaTSCAN imaging has a favorable benefit/risk profile in patients with movement disorders and/or dementia.

The benefits include more accurate and rapid diagnosis, reduced rates of misdiagnosis, and the potential for consequent improvements in treatment and management of patients. Data from 8 clinical studies, all of which showed a consistently benign safety profile for DaTSCAN, with relatively few Adverse Events (AE) and no Serious Adverse Events (SAE) that were considered related to DaTSCAN administration.

While there is always some risk associated with injection of radioactive material, levels of radiation exposure associated with the use of DaTSCAN are below the threshold of concern according to current public safety standards. Thus, it can be concluded that the benefits of DaTSCAN far outweigh the very minor risks of DaTSCAN.

1.5 Conclusion

Imaging with DaTSCAN provides a visual depiction of the functioning of nigrostriatal neurons. Disorders involving loss of nigrostriatal neurons show loss of signal on DaTSCAN images. When combined with the results of a clinical neurological assessment, this information may assist physicians in reaching earlier and more accurate diagnoses of patients with movement disorders and dementia. There is no intent to use this agent to diagnose a specific movement disorder or dementia type. DaTSCAN is intended for use solely as an adjunct to patient workup to supplement, and not replace, neurological examination and clinical judgment.

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3 LIST OF ABBREVIATIONS

Term	Meaning
AD	Alzheimer's disease
AE	Adverse event
BIE	Blinded image evaluation
CP	Consensus Panel
DaTSCAN	Injection of [^{123}I] ioflupane ([^{123}I]FP-CIT, [^{123}I]ß-CIT-FP)
DaT	Dopamine transporter
DLB	Dementia with Lewy Bodies
ECG	Electrocardiogram
ET	Essential tremor
FDA	U.S. Food and Drug Administration
ITD	Intent-to-Diagnose
L-DOPA	Levodopa
MBq	Megabecquerel
mCi	Millicurie
MHD	Maximum human dose
MSA	Multiple system atrophy
mSv	Millisieverts
NICE	National Institute for Clinical Excellence (UK)
PD	Parkinson's disease
PET	Positron emission tomography
PS	Parkinsonian syndrome
PSP	Progressive supranuclear palsy
REM	Rapid eye movement
SAE	Serious adverse event
SD	Standard deviation
SDD	Striatal dopaminergic deficit
SOC	System organ class
SOT	Standard of truth
SPECT	Single photon emission computed tomography
Sv	Sieverts
UKPDS	United Kingdom Parkinson's Disease Society
UPDRS	Unified Parkinson's disease rating scale

4 INTRODUCTION

DaTSCAN™ (Ioflupane I 123 Injection) is an intravenously administered diagnostic radiopharmaceutical. DaTSCAN is intended for use with single photon emission computed tomography (SPECT) imaging of the brain for detecting loss of functional nigrostriatal dopaminergic neurons defined in this document as a striatal dopaminergic deficit, or SDD. SDDs are known to occur in idiopathic Parkinson's disease (PD) and other parkinsonian syndromes (PS), but not in benign essential and dystonic tremors (see Table 1). Similarly, SDDs occur in dementia with Lewy bodies (DLB) but not in Alzheimer's disease (AD). The detection or exclusion of an SDD provides important information when diagnosing patients with movement disorders and dementia, and, in conjunction with other clinical information, allows the physician to reach an earlier and more accurate diagnosis [Marshall et al. 2009, Catafau et al. 2004, O'Brien et al. 2009]. The proposed indication for use of DaTSCAN in the United States is:

> *"DaTSCAN is a radiopharmaceutical containing [^{123}I]ioflupane, indicated for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration."*

4.1 Product History

European Regulatory History

DaTSCAN was granted a Marketing Authorization by the European Commission in July 2000 for the following indication:

> "detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain PS, in order to help differentiate Essential Tremor from PS related to idiopathic Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). DaTSCAN is unable to differentiate between PD, MSA and PSP."

In July, 2006 the following expansion to the European indication was approved:

> "DaTSCAN is also indicated to help differentiate probable DLB from Alzheimer's disease. DaTSCAN is unable to discriminate between DLB and PD dementia."

DaTSCAN is currently licensed and distributed in 32 countries. Over the last 9 years, more than 216,000 patients have been exposed to the product in clinical studies and the marketplace without any significant safety issues. DaTSCAN has shown an excellent safety profile, derived from both clinical studies and post-marketing experience.

US Regulatory History

Following several meetings with FDA, GE Healthcare submitted the New Drug Application for DaTSCAN on March 6, 2009. Due to an unmet clinical need for an imaging agent to assist physicians in managing patients according to their dopaminergic status, GE Healthcare has been granted "Priority Review" of the DaTSCAN drug application and an Advisory Committee Meeting has been scheduled for August 11, 2009.

5 MEDICAL NEED/RATIONALE FOR DaTSCAN

5.1 Medical Need

The basal ganglia are brain nuclei that modulate both movement and cognition; consequently, diseases that affect the basal ganglia result in movement disorders and cognitive dysfunction [Cote 1991; Martin 1996]. One part of the basal ganglia is the substantia nigra, a nucleus with pigmented dopaminergic neurons that project to, and synapse with, neurons in the striata; these neurons are collectively called the nigrostriatal pathway (see Figure 2). They are dopaminergic because dopamine is their predominant neurotransmitter.

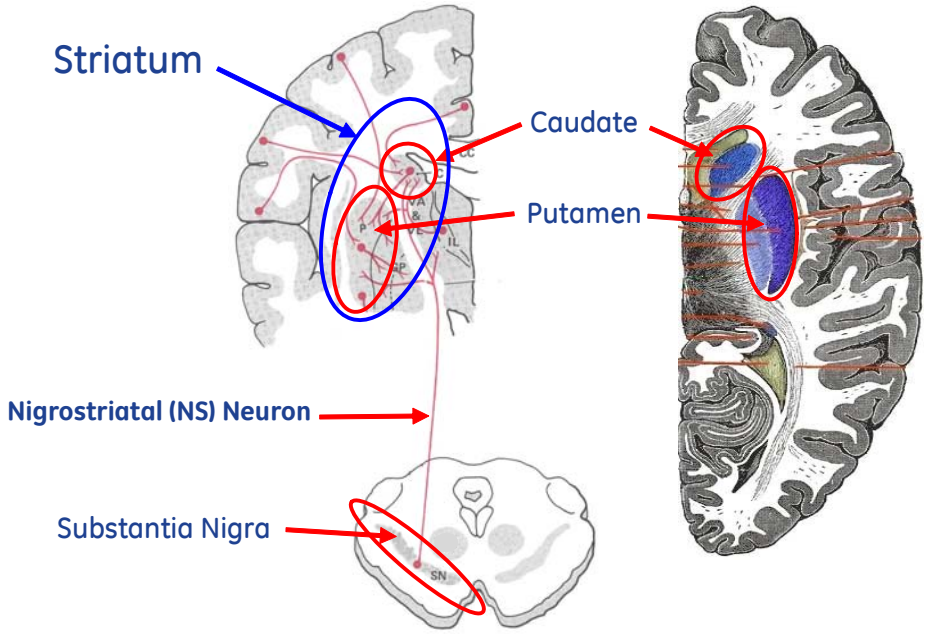

Figure 2 Diagrammatic representations of coronal sections of the human brain showing the dopaminergic neuron link between the substantia nigra (in the midbrain) and striata (in the forebrain)

The loss of nigrostriatal neurons and subsequent decrease in dopamine release at the striatal synapses, disrupts the motor control pathway through the cortex and results in parkinsonian signs such as tremor, rigidity, bradykinesia, and gait disturbance. However, this is not the only cause of parkinsonism or its signs, both of which are common among persons aged 65 and older [Bennett et al. 1996]. In their early stages, the signs of parkinsonian disorders may be similar to non-parkinsonian disorders such as essential tremor (ET) (Table 1).

Table 1 Classification of Movement Disorders by Presence/Absence of Striatal Dopaminergic Deficit

Movement Disorders with Striatal Dopaminergic Deficit	Movement Disorders without Striatal Dopaminergic Deficit
• Parkinson's disease (PD) [Victor, 2001; Fahn, 2003; Bernheimer et al. 1973; Ma et al. 1997; Pakkenberg et al. 1991; Rinne et al. 1989; Beal et al. 1994] • Multiple system atrophy (MSA) [Wenning et al. 1997; Kume et al. 1993] • Progressive supranuclear palsy (PSP) [Hardman et al. 1997] • Cortical-basal ganglionic degeneration [Fahn, 2003] • Parkinson-dementia-ALS complex of Guam [Fahn, 2003] • Diffuse Lewy body disease (DLBD) [Fahn, 2003]	• Essential Tremor [Rajput et al. 2004] • Secondary parkinsonism (due to drugs, toxins, infection, infarct, mass, normal-pressure hydrocephalus) [Fahn, 2003] • Progressive pallidal atrophy [Fahn, 2003] • Huntington's disease [Bernheimer et al. 1973] • Wilson's disease [Fahn, 2003] • X-linked dystonia-parkinsonism [Fahn, 2003]

Some, but not all, dementia types are also characterized by the presence of an SDD (Table 2).

Table 2 Classification of Dementia Types by Presence/Absence of Striatal Dopaminergic Deficit

Dementia Types with Striatal Dopaminergic Deficit	Dementia Types without Striatal Dopaminergic Deficit
• Dementia with Lewy bodies (DLB) [Piggott et al. 1998]	• Alzheimer's disease (AD) [Torack et al. 1992; Kemppainen et al. 2002] • Pick's disease [Yokota et al. 2002] • Huntington's disease [Bernheimer et al. 1973].

Accuracy of Clinical Diagnosis of Parkinsonian Movement Disorders

The diagnostic differentiation of Parkinsonian syndromes such as Parkinson's disease (PD) from other movement disorders such as essential tremor (ET) can be difficult, particularly in the early stages of these diseases when symptoms and signs are subtle [Litvan et al. 1998; Lees et al 2009]. The accuracy of clinical diagnoses has been evaluated in several clinicopathological studies using autopsy as a reference: up to 25% of patients diagnosed as having PD ultimately turned out to have another diagnosis [Ward and Gibb 1990; Hughes et al. 1992; Litvan et al. 1998; Hughes et al. 2001].

Movement disorder specialists are superior at diagnosing Parkinson's disease and other Parkinsonian syndromes compared to primary care physicians and non-specialist neurologists primarily because they make false positive diagnoses of PD less frequently [Kis et al. 2002, Jennings et al. 2004, Hughes et al. 2002].

Differentiating between PS and ET is important because they have different prognoses and are treated differently.

The consequences of misdiagnosis can be significant. A false positive diagnosis of dopamine deficient PS may result in patients receiving dopaminergic drugs unnecessarily, with potential for harm from adverse reactions. Hensman and Bain [2006] reported a case of dystonia-associated tremor, misdiagnosed as PS, which worsened progressively during 17 months of treatment with L-DOPA. There are several reports of patients with erroneous PS diagnoses being administered in appropriate therapy for up to 25 years [Hagenah et al. 1999; Marshall et al. 2006b] In a population-based study of therapy withdrawal, 4.7% of 610 patients taking antiparkinson medication for a diagnosis of PD were re-diagnosed with an alternative, non-dopamine-deficient tremor or parkinsonian disorder, and successfully stopped antiparkinson drugs without clinical deterioration [Newman et al. 2007].

Accuracy of Clinical Diagnosis of Dementias

The diagnostic differentiation of dementia syndromes such as Alzheimer's disease (AD) and vascular dementia from other causes of dementia such as dementia with Lewy bodies (DLB) can be challenging.

The accuracy of the clinical diagnosis of DLB has been evaluated in 9 clinicopathological studies that collectively studied 135 DLB patients and 350 non-DLB patients, using autopsy as the standard of truth (SOT). The results of these studies were summarized by Litvan [2003], who reported the average sensitivity (proportion of DLB patients that were correctly diagnosed clinically) to be 49% (range, 0% to 83%) and the average specificity (proportion of non-DLB patients that were correctly diagnosed clinically) to be 92% (range, 79% to 100%).

The impact of examiner experience does not appear to have been assessed yet for DLB. Nevertheless, it is a reasonable assumption that dementia specialists would be expected to perform better than community psychiatrists and neurologists, who would be expected to perform better than general practitioners.

Differentiating between DLB and AD or vascular dementia is important because of differences in treatment. Further, the use of antipsychotic drugs is relatively contraindicated in DLB because of serious drugs reactions that can be fatal [McKeith et al. 2005; Mosimann and McKeith 2003; Aarsland et al. 2005].

Summary of Medical Need

There is a medical need for an earlier, more accurate, and more reproducible diagnosis of parkinsonian disorders and dementias. Such a diagnosis would improve diagnostic confidence especially in early disease and reduce patient risks and costs from inappropriate antiparkinsonian or anti-psychotic medications.

5.2 Rationale for the Development of DaTSCAN

A non-invasive test to determine whether or not a patient has likely lost functional nigrostriatal neurons would be a helpful addition to clinical diagnosis.

In vivo molecular imaging, is a potential method to detect a loss of functional nigrostriatal dopaminergic neurons. Pre-synaptic striatal release of dopamine results in post-synaptic modulation of striatal dopaminergic neurons. After release, extracellular dopamine is also taken up by pre-synaptic DaT protein which internalizes dopamine for recycling in the nigrostriatal neuron. Loss of nigrostriatal neurons results in loss of DaT [Piggott et al. 1998] and would consequently be detected as a reduction in striatal DaT binding of an imaging agent. The density of DaT in the striatum enables the contrast between DaT-rich (striatal) and DaT-deficient (extrastriatal) regions.

Ioflupane is a cocaine analog with a selective affinity (0.6 to 30 µM) for the DaT and was developed for DaT imaging.

Autoradiographic studies using post-mortem human brain slices showed ioflupane binds preferentially to the DaT-rich striata [Lundkvist et al. 1995, Günther et al. 1997]. In both studies, the specificity of ioflupane binding was confirmed by a reduction in signal with known DaT inhibitors. Figure 3 depicts the density of ioflupane binding, with highest density in the striatum (caudate and putamen).

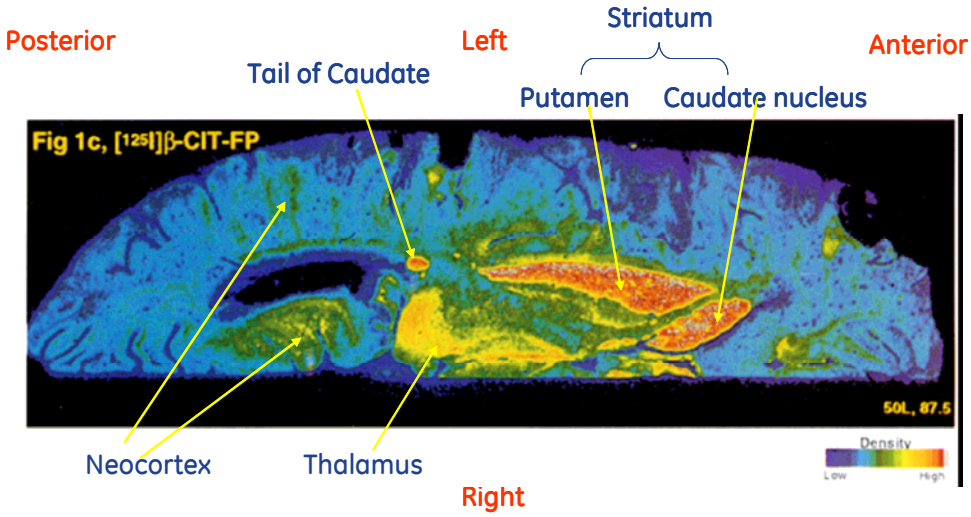

Figure 3 Autoradiogram of [^{125}I]ioflupane (β-CIT-FP) binding to human brain slice showing intense activity in the striatum (caudate and putamen) [after Günther et al. 1997]

In animal models of PD, where varying degrees of SDD were induced by the administration of toxins, the binding of [^{123}I]ioflupane has been correlated to markers of cell body number and function in the substantia nigra, functional dopaminergic neurons in the striatum and the severity of the induced parkinsonian behavioral symptoms [Alvarez-Fischer et al. 2007; Ashkan et al. 2007].

6 CLINICAL DEVELOPMENT PROGRAM

6.1 Summary of DaTSCAN studies

GE Healthcare has completed a total of 8 clinical studies with DaTSCAN. The data was initially used to support the European registration of DaTSCAN:

Phase 1: CY95.FP.I

Phase 2: CY96.FP.II and PDT02005

Phase 3: DP008-003, PDT304, PDT301 and PDT03007

Phase 4: PDT408

A full list of these studies is given in Table 3.

Described in Section 6.2.2 are recent results of an ongoing investigator-initiated study by Dr. Zuzana Walker, the aim of which is to confirm the correlation between a baseline DaTSCAN and the eventual neuropathologic diagnosis at autopsy, in order to definitively validate the efficacy of DaTSCAN for imaging an SDD.

In addition to the Walker study, three GE-sponsored Phase 3 studies (DP008-003, PDT304 and PDT301) have been defined as providing principal support for the registration of DaTSCAN in the United States as an agent to detect loss of functional nigrostriatal dopaminergic neurons. Two of these studies were conducted with patients with parkinsonian signs (DP008-003 and PDT304) and the third was with dementia patients (PDT301). Each of these studies is described in detail in Section 6.2.

A recent study which demonstrated the utility of DaTSCAN in the diagnosis and management of patients with clinically uncertain PS are described in Section 6.4.

Table 3 Summary of DaTSCAN Clinical Studies

Phase	Study Number	Title	Total Number of Subjects Dosed	Number of Healthy Volunteers Dosed	Number of Patients Dosed	Study Status
1	CY95.FP.I	A single-centre, open study of an intravenous dopamine transporter ligand containing 111 MBq [^{123}I]FP-CIT (DaTSCAN), in healthy volunteers to examine biodistribution, safety and tolerability	12	12	0	Completed
2	CY96.FP.II	A single-centre, open study of an intravenous dopamine transporter ligand, containing 111 MBq [^{123}I]FP-CIT (DaTSCAN), in healthy volunteers and patients with Parkinson's disease to examine uptake kinetics in various brain regions and safety	30	10	20	Completed
2	PDT02005	An open, single-centre, phase 2, clinical and imaging study to assess the striatal uptake of an intravenous solution, DaTSCAN, containing a dopamine transporter radio-ligand in subjects with vascular parkinsonism compared to subjects with cerebrovascular disease	50	0	50	Completed
3	DP008-003	A multi-centre, phase 3, clinical study to compare the striatal uptake of an intravenous solution containing a dopamine transporter radio-ligand, [^{123}I]FP-CIT (DaTSCAN), in patients diagnosed with Parkinson's disease, Multiple System Atrophy, Progressive Supranuclear Palsy and definite essential tremor	224	35	189	Completed
3	PDT304	An open, phase 3, clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN, in patients with early parkinsonism	179	0	179	Completed
3	PDT03007	A phase 3, multi-centre, open clinical study to assess the striatal uptake of intravenous DaTSCAN, to monitor progression, in healthy volunteers and subjects previously diagnosed with parkinsonian syndrome and Essential Tremor, by SPECT imaging	31	8	23	Completed
3	PDT301	An open-label, phase 3, clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN, in subjects with dementia with Lewy Bodies	326	0	326	Completed
3	Walker	Investigation of Changes in the Dopamine Transporter Using DaTSCAN™ SPECT in Dementia with Lewy Bodies, Other Dementias and Parkinson's Disease	80	16	64	Ongoing
4	PDT408	A phase 3b/4, multi-centre, open label clinical study to assess the striatal uptake of intravenous DaTSCAN (^{123}Ioflupane injection) in subjects with clinically uncertain parkinsonian syndromes	120	0	120	Completed
4	PDT409	A multi-centre, randomized, open label, comparative phase 4 trial to assess changes in clinical management after DaTSCAN imaging of subjects with clinically uncertain parkinsonism in a general neurologist setting	100*/125	0	100*	In progress
	TOTAL		1,152	81	1,071	

*Estimated as of June 2009 based on enrollment of 201 subjects with 1:1 randomization to dosing or a $\geq$ 1 year wait

6.2 Summaries of Phase 3 Efficacy Studies

6.2.1 Background

DATSCAN has been extensively studied in healthy volunteers as well as in subjects with signs of PS and dementia (Table 3).

Knowledge of the appearance of normal DaTSCAN images was gained through Phase 1 and Phase 2 studies (CY95.FP.I, CY96.FP.II) that enrolled healthy volunteers.

The ability of DaTSCAN images to differentiate between subjects with movement disorders known to involve loss of nigrostriatal neurons and subjects without such disorders was demonstrated in Phase 2 studies (CY96.FP.II and PDT02005).

Prior to the design of the Phase 3 efficacy studies, multiple autopsy studies had confirmed that loss of at least 50-60% of nigrostriatal neurons occurs before symptom onset in PS [Fearnley and Lees 1991], and that a neuronal loss of at least 30% occurs prior to symptom onset in DLB [Piggott et al. 1998]. The obvious SDDs seen by visual inspection of DaTSCAN images could therefore be predicted and the four Phase 3 studies of efficacy described below demonstrate that the agent can routinely differentiate between subjects with and without an SDD.

6.2.1.1 Elements Common to the Efficacy Studies

Procedures common to the described studies were the injection of 3 to 5 mCi (111 to 185 MBq) of DaTSCAN intravenously followed by SPECT brain imaging for 30 to 40 minutes between 3 and 6 hours post-injection.

A visual assessment of the DaTSCAN striatal image provided a categorization as either normal (negative; no SDD) or abnormal (positive; SDD present).

Each DaTSCAN image assessment was compared to the presumed classification (positive or negative for an SDD) of the subject's Standard of Truth (SOT) diagnosis, and the image assessment was then classified as a True Positive, True Negative, False Positive, or False Negative. Sensitive and specificity were then determined. Sensitivity was calculated by dividing the number of subjects with True Positive image assessments by the number of subjects with a diagnosis presumed positive for an SDD. Specificity was calculated by dividing the number of subjects with True Negative image assessments by the number of subjects with diagnoses presumed not to involve an SDD.

The efficacy studies differed by the population of interest, the type of image interpretation (blinded or unblinded to clinical information), and the SOT as discussed below.

6.2.1.2 Discussion on the Standard of Truth used for DaTSCAN Studies

The GE-sponsored Phase 3 efficacy studies were designed to test the value of DaTSCAN SPECT imaging for detecting or excluding an SDD in patients with signs of movement

disorders or dementia. Given the large sample sizes required for the studies, autopsy confirmation of diagnoses was not deemed practical. Therefore, the SOT used in these studies was expert clinical diagnosis, based whenever possible on validated consensus criteria. A summary of the clinical diagnostic criteria used as the SOT in each study is presented in Table 4, along with a brief description of the clinicopathologic study which validated the criteria. For all the disease types included in the GE-sponsored efficacy studies, except for Multiple System Atrophy, there has been extensive validation of clinical diagnostic criteria against autopsy findings. Hence, all three of these studies are deemed valid to demonstrate the accuracy of DaTSCAN to determine a dopaminergic deficit.

Although the use of expert clinical diagnosis as a SOT is considered acceptable because of published correlations with autopsy, the ultimate study could be viewed as performing a baseline DaTSCAN and then prospectively following the patients to autopsy. Such a study is actually being performed and is led by the investigator, Dr. Zuzana Walker and colleagues (see Section 6.2.2).

Table 4 Validation of Clinical Diagnostic Criteria Used as the Standard of Truth in DaTSCAN Studies

Diagnosis	Studies	Clinical Diagnostic Criteria	Description of Clinicopathologic Validation Study
Parkinson's Disease (PD)	DP008-003 PDT304	• UKPDS Brain Bank Clinical Criteria [Gibb and Lees, 1988a]. • Patients also had to meet the UKPDS Brain Bank Clinical Criteria Step 1 for parkinsonism	100 patients autopsied who had been prospectively diagnosed clinically with PD during life by consulting neurologists. Retrospective application of UKPDS Brain Bank criteria gave diagnostic accuracy of 82% [Hughes et al., 1992].
Parkinson's Disease (PD)	PDT304	• Unified Parkinson's disease rating scale (UPDRS) Part III score	UPDRS part III score were correlated with autopsy findings of 18 patients who had been diagnosed during life with clinical parkinsonism and in 5 age-matched controls. Measurements of neuronal density in the substantia nigra were negatively correlated with UPDRS-III score (correlation coefficient $r = -0.83$; $p < 0.001$); the higher UPDRS score, the lower the neuronal density, indicating greater loss of nigrostriatal neurons [Greffard et al. 2006].
Progressive Supranuclear Palsy (PSP)	DP008-003	• National Institute of Neurological Disorders and Stroke Society for probable PSP (NINDS-SPSP) [Litvan et al. 1996b] • Patients also had to meet the UKPDS Brain Bank Clinical Criteria Step 1 for parkinsonism	Autopsy was applied as SOT and the diagnostic criteria have been shown to have sensitivity of 50% and specificity of 100% [Litvan et al. 1996b].
Essential Tremor (ET)	DP008-003	• Findley and Koller [1994]	Two studies reported autopsy findings in subjects diagnosed with ET using criteria very similar or identical to those of Findley and Koller. Rajput et al. reported autopsy results for 20 patients diagnosed during life with ET. 6 of the 20 patients had clinical signs of PS in addition to ET. Signs of PSP were seen in 2 and PD seen in 1 patient. Of the 14 patients without clinical signs of PS, no pathology was seen in the substantia nigra. 14 out of 14 (100%) of patients who met the Findley and Koller criteria for ET with no signs of PS were free of pathology in the substantia nigra [Rajput et al. 2004]. Louis et al. reported autopsy findings in 33 ET cases (1 diagnosed with PD) and 21 controls. In only 2 cases was a neuropathological diagnosis of PD made. In this study 31 (94%) of 33 patients with ET were found to be free of PD [Louis et al. 2007].
Dementia with Lewy Bodies (DLB)	PDT301	• International Consensus Criteria [McKeith et al. 2000]	Diagnoses using the criteria were compared to autopsy diagnoses in 26 patients with possible or probable DLB, 19 patients with Alzheimer's disease, 5 with vascular dementia, 1 patient with PSP. The criteria had a sensitivity of 83% and specificity of 95% for diagnosing DLB [McKeith et al. 2000].

Table 4 Validation of Clinical Diagnostic Criteria Used as the Standard of Truth in DaTSCAN Studies

Diagnosis	Studies	Clinical Diagnostic Criteria	Description of Clinicopathologic Validation Study
Multiple System Atrophy (MSA)	DP003-003	• Consensus Committee of the American Autonomic Society. American Academy of Neurology [1996] • Patients also had to meet the UKPDS Brain Bank Clinical Criteria Step 1 for parkinsonism	No evidence was found that these criteria have been validated by autopsy studies.
Parkinsonian Syndrome (PS)	DP008-003	• UKPDS Brain Bank Clinical Criteria Step 1 [Gibb and Lees, 1988a]	The SOT endpoint for the study was whether or not each subject had PS, according to the UKPDS Brain Bank criteria step 1. PS includes PD, PSP and MSA.

6.2.2 The Walker Study - Dementia

The Walker investigator-initiated study is a prospectively designed clinicopathological study to assess the accuracy of DaTSCAN imaging by following a cohort of imaged subjects to death so that a comparison can be made with a definitive pathological diagnosis made at autopsy.

Objective

The primary objective is to determine the sensitivity and specificity of DaTSCAN image assessments in patients with dementia, using autopsy as the SOT, with PD patients and healthy volunteers enrolled as controls.

Design

The Walker study is an ongoing single-dose study of DaTSCAN started in June 1996 and being conducted at University College London. As autopsy results accrue, results are periodically analyzed and published [Walker et al.1999, 2007]. The results reported here are based on the latest available autopsy data as of July, 2009.

Population

Subjects with a diagnosis of AD, PD, or DLB who not been exposed to any anti-parkinsonian medication at the time of imaging were enrolled with healthy age-matched controls. Control subjects could not be taking any drug(s) known to affect the dopaminergic system.

Subjects were diagnosed clinically at baseline using published criteria for DLB [McKeith et al. 1996], AD [McKhann et al.1984], or PD [Hughes et al.1992]. If a subject met the criteria for both AD and DLB, they were categorized as a DLB subject.

Methods

Image Evaluations:

Images were presented in random order to 3 readers blinded to both the clinical and autopsy diagnoses, who viewed the images alone and then in consensus. The consensus decision was used for the subsequent analyses. Scans were assessed visually and scored as normal or abnormal for the primary analysis.

Standard of Truth:

The neuropathological diagnosis at autopsy was the SOT. Criteria for a neuropathological diagnosis of DLB included the presence of Lewy bodies, degree of neuron loss, and degree of loss of pigment in the substantia nigra.

Results

Subject Demographics:

Eighty subjects with the following baseline clinical diagnoses were enrolled between 1996 and 1999:

- Dementia (44): DLB (27) and AD (17)
- Corticobasilar degeneration (1)
- PD (19)
- Healthy controls (16)

Subjects were followed prospectively after DaTSCAN imaging. As of the date of preparation of this document, 28 subjects have undergone autopsy, 22 are known to still be alive, and 30 have either been lost to follow-up or died and permission was not given for autopsy. Of the 28 who have undergone autopsy, results are available from 27, who had the following baseline diagnoses:

- AD (7)
- DLB (14)
- Corticobasilar degeneration (1)
- PD (4)
- Healthy control (1)

Characteristics of the 27 autopsied subjects are in Table 5.

Table 5 Demographic Characteristics at Baseline for Autopsied Patients

Variable	Statistic	N = 27
Age at onset of dementia (yr)	n Mean (SD) Median Min, Max	26 73.1 (9.34) 73.0 53, 93
Age at time of DaTSCAN (yr)	n Mean (SD) Median Min, Max	27 76.4 (8.55) 77.0 58, 95
Age at death (yr)	n Mean (SD) Median Min, Max	27 79.9 (9.21) 81.0 60, 100
Gender	Male, n (%) Female, n (%)	18 (66.7) 9 (33.3)
Baseline clinical diagnosis classification	SDD, n (%) No SDD, n (%)	18 (66.7) 9 (33.3)

SDD = striatal dopaminergic deficit; SD = standard deviation; n = number of subjects in each category; N = total number of subjects; min = minimum; max = maximum.

Efficacy:

There was excellent correlation between the DaTSCAN image assessments and the autopsy findings as summarized in Table 6. Based on these data, the sensitivity and specificity of DaTSCAN image assessments were 84.6% and 85.7%, respectively.

Table 6 Classification of the Neuropathological Diagnosis at Autopsy (SOT) Versus the Visual Assessment of the DaTSCAN™ Image – The Walker Study

	Classification of the Neuropathological Diagnosis at Autopsy (Standard of Truth)		
Visual Image Assessment	**SDD n (%)**	**No SDD n (%)**	**Total n (%)**
Normal (No SDD)	2	12	14
Abnormal (SDD)	11	2	13
Total	13	14	27

n = number of subjects in each category; SDD = striatal dopaminergic deficit.
Percentage based on the number of subjects with both evaluations.

The two false-positive subjects both had a clinical diagnosis of DLB and abnormal DaTSCAN images, but other diagnoses were found at autopsy (AD with cerebrovascular dementia, and frontotemporal dementia).

The two false-negative subjects both had a baseline diagnosis of DLB with normal DaTSCAN images. At autopsy, both were found to have DLB.

For comparison, the correlation of the baseline clinical diagnoses of these patients and the autopsy findings is summarized in Table 7, and the corresponding sensitivity and specificity of the baseline clinical diagnosis are 84.6% and 50.0%.

Table 7 Classification of the Neuropathological Diagnosis at Autopsy (SOT) Versus the Initial Clinical Diagnosis – The Walker Study

	Classification of the Neuropathological Diagnosis at Autopsy (Standard of Truth)		
Clinical Diagnosis	**SDD n (%)**	**No SDD n (%)**	**Total n (%)**
SDD	11	7	18
No SDD	2	7	9
Total	13	14	27

n = number of subjects in each category; SDD = striatal dopaminergic deficit.
Percentage based on the number of subjects with both evaluations.

This study demonstrated that DaTSCAN image assessments had an excellent correlation with autopsy findings in detecting loss of functional nigrostriatal neurons. Both DaTSCAN images

and baseline clinical diagnosis had similar sensitivity; however, specificity was markedly higher for the DaTSCAN images. The two false negative DaTSCAN images involved DLB, which may involve lesser degrees of neuronal loss than Parkinsonian movement disorders.

6.2.3 Study DP008-003 - Movement Disorders

Objective

The primary objective was to determine the sensitivity and specificity of DaTSCAN images in differentiating between subjects with and without a PS in the Intent-to-Diagnose (ITD) population.

Design

Study DP008-003 was a multicenter, Phase 3 study to assess striatal uptake of DaTSCAN in subjects with a known diagnosis of a PS compared to subjects with ET and healthy volunteers. This study was conducted between August, 1997 and February, 1998. Six European sites participated: 2 in Germany, 2 in the UK, and 1 each in The Netherlands and Belgium.

Population

The study population comprised male and female patients aged 40 to 80 years with:

(1) A PS diagnosed clinically using diagnostic criteria [Gibb and Lees, 1988b] that had been correlated with autopsy [Hughes et al., 1992]. In addition, subjects had to meet published consensus criteria for the diagnosis of a specific PS: PD [Gibb and Lees, 1988b], MSA [AAN, 1996], or PSP [Litvan et al., 1996a], or

(2) ET according to the Findley & Koller criteria [1994], or

(3) Healthy volunteers aged 50 to 80 years.

Methods

Image Evaluations:

Images were evaluated by on-site study personnel and also in a separate Blinded Image Evaluation (BIE). The primary endpoint was the on-site visual assessment of the DaTSCAN image as normal or abnormal.

The BIE panel consisted of 5 of the investigators who evaluated each DaTSCAN image visually for striatal uptake in accordance with the definitions defined in Table 8.

Table 8 DaTSCAN Visual Image Assessment Classifications

DaTSCAN™ Image Classification	Criteria
Normal	Normal images were characterized by uptake of the tracer in both right and left putamen and caudate nuclei. The image was largely symmetrical with approximately equal levels of uptake on both left and right sides. Activity was contained close to the center of the image forming 2 crescent shaped areas of uptake.
Abnormal, type 1	Uptake was asymmetric with normal or almost normal putamen activity in 1 hemisphere and a more marked change on the other side.
Abnormal, type 2	Uptake was significantly reduced in the putamen on both the right and left sides. Activity was confined to the caudate nuclei and forms 2 roughly symmetrical, circular areas.
Abnormal, type 3	Uptake was virtually absent from both putamen and caudate nuclei on each side of the brain resulting in a significant reduction in contrast and the visualization of background activity throughout the rest of the image.

For analysis, the 3 subtypes of abnormal were pooled into an "abnormal" category. A majority assessment was made for each patient based on the verdict of at least 3 of the readers.

Standard of Truth:

The SOT for judging the accuracy of the DaTSCAN image assessments was the expert clinical diagnosis of the patient made at baseline. Subjects with PS were presumed positive for an SDD, and subjects with ET and the healthy volunteers were presumed negative for an SDD.

Results

Subject Demographics:

Subject demographics for this study are summarized in Table 9. There were no notable differences in demographics between the groups.

Table 9 Summary of Subject Demographics – Safety Population – Study DP008-003

Variable	Statistic	Overall (N=224)	Diagnosis					
			Healthy Volunteer (no SDD) (N=35)	Essential Tremor (no SDD) (N=29)	Parkinson's Disease (SDD) (N=132)	MSA (SDD) (N=18)	PSP (SDD) (N=10)	PS (PD, MSA, PSP) (SDD) (N=160)
Gender								
Male	n (%)	137 (61%)	15 (43%)	20 (69%)	87 (66%)	10 (56%)	5 (50%)	102 (64%)
Female	n (%)	87 (39%)	20 (57%)	9 (31%)	45 (34%)	8 (44%)	5 (50%)	58 (36%)
Race								
Caucasian	n (%)	220 (98%)	33 (94%)	29 (100%)	131 (99%)	17 (94%)	10 (100%)	158 (99%)
Black	n (%)	3 (1%)	2 (6%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	1 (1%)
Asian	n (%)	1 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Age (yr)	n	224	35	29	132	18	10	160
	Mean (SD)	63 (9)	61 (9)	64 (9)	63 (9)	61 (8)	68 (4)	63 (9)
	Min, Max	40, 80	41, 79	46, 80	40, 80	46, 72	62, 76	40, 80
	Median	63	60	65	63	63	66	64
Weight (kg)	n	215	35	28	126	16	10	152
	Mean (SD)	73 (14)	74 (12)	75 (20)	72 (12)	76 (15)	70 (10)	72 (12)
	Min, Max	38.1, 130.0	53.0, 108.0	38.1, 130.0	47.0, 109.8	50.0, 100.0	54.4, 85.0	47.0, 109.8
	Median	72	73	76	71	76	71	71

N = number of subjects dosed; n = number of subjects with the respective demographic information; SD = standard deviation; MSA = Multiple System Atrophy; PSP = Progressive Supranuclear Palsy; PS = parkinsonian syndrome; PD = Parkinson's disease; SDD = striatal dopaminergic deficit. Safety population included subjects who received any amount of DaTSCAN.

Within the PD population there was a range of disease severity as reflected by the Hoehn and Yahr scores (Table 10).

Table 10 Summary of Screening Characteristics – Safety Population – Study DP008-003

H&Y Stage	Statistic	Overall (N=224)	Diagnosis				
			Healthy Volunteer (N=35)	Essential Tremor (N=29)	Parkinson's Disease (N=132)	MSA (N=18)	PSP (N=10)
1	n (%)	34 (15%)	0 (0%)	0 (0%)	34 (26%)	0 (0%)	0 (0%)
2	n (%)	46 (21%)	0 (0%)	0 (0%)	46 (35%)	0 (0%)	0 (0%)
3	n (%)	29 (13%)	0 (0%)	0 (0%)	24 (18%)	3 (17%)	2 (20%)
4	n (%)	24 (11%)	0 (0%)	0 (0%)	22 (17%)	1 (6%)	1 (10%)

N = number of subjects dosed; n = number of subjects with the respective demographic information; MSA = Multiple System Atrophy; PSP = Progressive Supranuclear Palsy; H&Y= Hoehn & Yahr.
Safety population included subjects who received any amount of DaTSCAN.

Efficacy:

Comparison of the on-site image assessments to the SOT (Table 11) resulted in values for sensitivity and specificity of 97.5% and 98.4%, respectively.

Table 11 Efficacy of On-Site DaTSCAN Image Read – Study DP008-003

On-Site DaTSCAN Image Visual Assessment	Clinical Diagnosis (Standard of Truth)		Total n (%)
	Parkinsonian Syndrome n (%)	Non-Parkinsonian Condition n (%)	
Abnormal (SDD Present)	154 (70%)	1 (0%)	155 (70%)
Normal (SDD Absent)	4 (2%)	61 (28%)	65 (30%)
Total	158 (72%)	62 (28%)	220

n = number of subjects in each category; SDD = striatal dopaminergic deficit.
Percentage based on the number of subjects with both evaluations.

The individual reader and majority BIE results (Table 12) were similar to the on-site results.

Table 12 Efficacy of DaTSCAN BIE by Reader and Majority Rating – Study DP008-003

Blinded Reader	Sensitivity	Specificity
A	93%	94%
B	97%	81%
C	96%	92%
D	92%	97%
E	94%	92%
Majority	95%	94%

Inter-reader agreement between the 5 BIE readers, as measured by Cohen's $_k$, ranged from 0.83 to 0.92, with a perfect correlation being 1.0; the pooled coefficient for all 5 readers was 0.87. Comparison of each BIE reader's results to the on-site readers' results gave Cohen's κ values ranging from 0.88 to 0.94.

The results of both the on-site and majority BIE image assessments compared with the clinical diagnosis for the ITD population analyses showed that the visual assessment of DaTSCAN images had high sensitivity and specificity for detecting or excluding an SDD in patients with signs of movement disorders.

6.2.4 Study PDT304 - Movement Disorders

Objective

The primary objective was to determine the sensitivity and specificity of baseline DaTSCAN images in differentiating between subjects with and without a PS in the ITD population.

Design

Study PDT304 was a multicenter, Phase 3 study to assess the predictive value of DaTSCAN imaging in differentiating between subjects with early symptoms and signs of movement disorders, specifically parkinsonism, other benign causes of tremor, and healthy volunteers. This study was conducted between January, 1999 and June, 2005. Ten European sites participated: 4 in the UK, 2 in Spain, and 1 each in Austria, Belgium, Germany and Portugal.

Population

The study population comprised male and female patients aged 30 to 90 years with:

(1) A Parkinsonian syndrome

(2) Undiagnosed movement disorders: likely early PD or ET.

- UPDRS part III (motor) scoring of 16 or less, for groups 1 and 2

(3) Healthy volunteers aged 30 to 49 years.

Methods

Image Evaluations:

DaTSCAN images were acquired at baseline, 18 and 36 months. The primary endpoint was blinded image assessment of the baseline DaTSCAN image by 3 independent blinded readers as normal or abnormal. The BIE readers classified each image set as normal, abnormal, or other if an image could not be assigned to any of the specific categories.

Standard of Truth:

The final SOT was the expert clinical diagnosis established by 2 independent movement disorder specialists in consensus, based on the assessment of a video of the patient's clinical examination recorded at 36 months. Similar assessments were also carried out at 18 months (interim SOT). The SOT was used to judge whether or not a subject had an SDD.

Results

Subject Demographics:

Table 13 presents the demographic characteristics by SOT diagnosis.

Table 13 Summary of Subject Demographics – Safety Population – Study PDT304

Variable		Overall (N=179)	Standard of Truth Diagnosis (Month 36)			
			Probable PD (N=66)	Possible PD (N=5)	Non-PD (N=31)	No Diagnosis (N=77)
		n (%)	n (%)	n (%)	n (%)	n (%)
Gender n (%)	Male	102 (57)	34 (52)	2 (40)	21 (68)	45 (58)
	Female	77 (43)	32 (48)	3 (60)	10 (32)	32 (42)
Race n (%)	Caucasian	179 (100)	66 (100)	5 (100)	31 (100)	77 (100)
Age (Years)	Mean (SD)	62 (11)	61 (10)	69 (9)	57 (13)	63 (11)
	Min, Max	33, 86	43, 78	57, 79	33, 79	34, 86
	Median	63	61	67	58	64
Weight[a] (kg)	Mean	73 (13)	72 (13)	66 (13)	78 (14)	73 (13)
	Min, Max	45.0, 116.0	45.0, 103.0	49.0, 81.0	57.2, 116.0	47.5, 112.0
	Median	73	73	70	79	72

N = number of subjects dosed; n = number of subjects with the respective demographic information; SD = standard deviation; PD = Parkinson's Disease.
Percentages are based on the safety population.
Safety population includes all subjects dosed.
[a] Height and weight missing for 1 probably PD subject and 1 subject with no diagnosis.

The on-site UPDRS score for the total efficacy population increased over time. The probable PD subjects showed an increase from a mean UPDRS score of 10.8 at baseline to 20.3 at 36 months, whereas the UPDRS score in the non-PD group remained stable over time: 6.4 at baseline and 7.1 at 36 months. The increase in mean UPDRS scores over time in the probable PD subjects is consistent with the known natural history of PD. Conversely, the lack of increase in UPDRS scores in the non-PD group is consistent with the natural history of ET.

Efficacy

Comparison of the BIE reader assessments to the SOT resulted in sensitivity of 77% to 79%, depending on the image reader. The specificity was 97% for all 3 independent readers. The mean sensitivity was 78% and the mean specificity was 97%.

Table 14 Baseline SPECT BIE Assessment by Reader Versus the Final (36-Month) SOT Diagnosis – ITD Population – Study PDT304

Baseline SPECT BIE Assessment	36-Month SOT Diagnosis			Total n (%)
	Probable PD (SDD) n (%)	Possible PD (SDD) n (%)	Non-PD (No SDD) n (%)	
Reader A				
Abnormal (SDD)	55 (54)	0 (0)	1 (1)	56 (55)
Normal (No SDD)	11 (11)	5 (5)	30 (29)	46 (45)
Total	66 (65)	5 (5)	31 (30)	102
Reader B				
Abnormal (SDD)	53 (54)	0 (0)	1 (1)	54 (55)
Normal (No SDD)	10 (10)	5 (5)	30 (30)	45 (45)
Total	63 (64)	5 (5)	31 (31)	99
Reader C				
Abnormal (SDD)	55 (54)	0 (0)	1 (1)	56 (55)
Normal (No SDD)	10 (10)	5 (5)	30 (30)	45 (45)
Total	65 (64)	5 (5)	31 (31)	101

n = number of subjects in each category; SDD = striatal dopaminergic deficit; PD = Parkinson's Disease; SOT = standard of truth; BIE = blinded image evaluation.
Percentage based on the number of subjects with both evaluations.
ITD = Subjects who underwent SPECT imaging after receiving DaTSCAN™ and underwent the 36-month SOT assessment.

On-site clinicians at baseline showed a tendency to over-diagnose an SDD (as indicated by the clinical diagnosis of PD). The sensitivity was high (93.0%), whereas the specificity was low (51.6%), indicating a high false-positive rate.

Comparison of the SPECT reads at baseline, 18 and36 months to the baseline SPECT read at revealed no large differences, showing that DaTSCAN images were very consistent over time.

The rates of inter-reader agreement among the 3 blinded readers were extremely high ($_k$ between 0.98 and 1.00). This, together with the stability of the image findings over time, verifies the robustness of the visual assessment.

The kappa value for agreement between the 2 clinical expert video readers, used to determine the SOT, was 0.37 at 18 months and 0.68 at months suggesting greater diagnostic accuracy with longer disease duration. The agreement between the clinical experts for clinical diagnosis was notably lower than of the inter-reader agreement for interpretation of DaTSCAN images.

This study showed DaTSCAN images to have high sensitivity and specificity in detecting an SDD in patients with signs of early and possible PS.

6.2.5 Study PDT301 - Dementia

Objective

The primary objective was to determine the sensitivity and specificity of DaTSCAN images in differentiating between subjects with and without probable DLB.

Design

Study PDT301 was an open-label, non-randomized, multicenter, single-dose Phase 3 clinical study to assess striatal uptake of DaTSCAN in subjects with dementia. This study was conducted between November 2003 and June 2006. Forty European sites participated: 12 in Germany, 8 in the UK, 4 in Austria, 4 in Italy, 4 in Spain, 2 in France, 2 in Norway, 2 in Sweden, and 1 each in Czech Republic and Portugal.

Methods

Images were evaluated both on-site and in a separate BIE with 3 independent readers. The primary endpoint was the blinded visual assessment of the DaTSCAN image as normal or abnormal for the ITD population.

Standard of Truth:

The SOT was the expert clinical diagnosis as established by an independent Consensus Panel composed of 3 experts in dementia. The panel reviewed all patient data with the exception of DaTSCAN images and applied diagnostic criteria that had been correlated with autopsy findings [McKeith et al. 2000]. Patients were categorized as having possible DLB, probable DLB, no DLB, or no diagnosis. A diagnosis of probable DLB was presumed to indicate the presence of an SDD, and a diagnosis of no DLB was presumed to indicate the absence of an SDD. The study included 2 SOT assessments by the consensus panel. The primary assessment was at baseline and the other was at 12 months.

Results

Subject Demographics

Subject demographics for this study are summarized in Table 15.

Table 15 Summary of Subject Demographics—Safety Population – Study PDT301

Variable	Statistic	Overall (N = 326)	Subject Disease Classification (Standard of Truth Diagnosis)			
			Probable DLB (N = 94)	Possible DLB (N = 57)	Non-DLB (N = 147)	No Diagnosis (N = 28)
Gender						
Male	n (%)	187 (57)	59 (63)	36 (63)	73 (50)	19 (68)
Female	n (%)	139 (43)	35 (37)	21 (37)	74 (50)	9 (32)
Race						
Caucasian	n (%)	326 (100)	94 (100)	57 (100)	147 (100)	28 (100)
Age (Years)	n	326	94	57	147	28
	Mean (SD)	73.9 (7.17)	73.8 (6.60)	74.4 (6.91)	74.4 (7.35)	70.5 (7.97)
	Min, Max	54, 90	54, 88	61, 90	55, 89	54, 84
	Median	75.0	74.0	75.0	75.0	73.5
Height (cm)	n	324	93	57	146	28
	Mean (SD)	167.9 (9.17)	167.6 (8.84)	168.8 (9.03)	167.2 (9.62)	170.4 (7.90)
	Min, Max	131, 195	148, 190	151, 192	131, 195	158, 188
	Median	168.0	168.0	170.0	167.0	172.0
Weight (kg)		323	93			
	n	71.41	69.88	56	146	28
	Mean (SD)	(13.301)	(14.615)	71.98 (12.967)	71.44 (12.631)	75.17 (12.623)
	Min, Max	33.0, 120.0	44.0, 120.0	40.0, 103.0	45.0, 113.0	33.0, 95.0
	Median	71.00	70.00	74.00	70.00	77.00
BMI		321	92			
	n	25.26	24.78	56	145	28
	Mean (SD)	(3.900)	(4.228)	25.18 (3.507)	25.50 (3.886)	25.80 (3.607)
	Min, Max	13.2, 40.6	17.0, 40.6	15.6, 35.5	17.3, 40.0	13.2, 32.1
	Median	25.03	24.44	25.50	25.18	26.08

SD = standard deviation; BMI = body mass index; DLB = dementia with Lewy bodies; Min = minimum; Max = maximum; N = number of subjects dosed; n = number of subjects with the respective demographic information.

Efficacy:

Table 16 presents sensitivity and specificity by blinded reader as well as the mean across the 3 readers for the ITD population. Using the first Consensus Panel (CP) diagnosis as the SOT, the mean sensitivity and specificity were 78% and 90%, respectively.

Table 16 Efficacy of DaTSCAN BIE by Reader and Mean– Study PDT301

Blinded Reader	Sensitivity	Specificity
A	80%	91%
B	75%	88%
C	80%	90%
Mean	**78%**	**90%**

Using the 12-month CP diagnosis as the SOT, the mean sensitivity and specificity were similar at 78% and 93%, respectively.

This study demonstrated that DaTSCAN had high sensitivity and specificity in differentiating between subjects with and without DLB.

6.3 Pooled Phase 3 Study Results

In the three GE-sponsored Phase 3 clinical efficacy studies described above (DP008-003, PDT304, and PDT301), a total of 648 patients with signs and symptoms of movement disorders (N = 322) or dementia (N = 326) were administered DaTSCAN.

The above results were pooled in a post-hoc analysis in order to provide more accurate overall estimates of the sensitivity and specificity of the visual assessment of DaTSCAN images for detecting an SDD. Since DaTSCAN detects an SDD and this abnormality is common to parkinsonian movement disorders and DLB, pooling across these studies is considered reasonable. Presented in Table 17 are the mean values of these parameters for the pooled population, the subset of patients with signs and symptoms of movement disorders, and the subset of patients with signs and symptoms of dementia. The results indicate that the sensitivity and specificity of DaTSCAN are both approximately 90% for detecting an SDD in the study population.

Table 17 Pooled Analyses of DaTSCAN Images for Detecting Loss of Nigrostriatal Dopaminergic Neurons - Study PDT301

	Subjects with Symptoms & Signs of Movement Disorders (N = 322)			Subjects with Symptoms & Signs of Dementia (N = 326)	Pooled Population (N = 648)
	DP008-003	PDT304	Pooled Movement Disorders	PDT301	All
True Positive Rate (Sensitivity)[a]	95%	78%	91%	79%	89%
True Negative Rate (Specificity)[a]	94%	97%	92%	90%	91%

[a]For detecting loss of nigrostriatal dopaminergic neurons

6.4 DaTSCAN Clinical Utility Study (PDT408)

Objective

This study assessed the ability of DaTSCAN to increase the diagnostic confidence in PS and identified cases in which a DaTSCAN image had an impact on patient management plans.

Design

This was a multi-center, open-label Phase 4 study. It was conducted between November 2000 and Jan 2002 at 15 sites in 8 European countries: 2 in Belgium, 2 in France, 3 in Germany, 2 in Italy, 1 in Portugal, 2 in Spain, 2 in the UK, and 1 in Austria.

Methods

Image Evaluations:

Images were assessed by the on-site nuclear medicine physician, who classified them as normal or abnormal.

Standard of Truth:

The SOT in this study was the final diagnosis made at 24 months based on all available data, including the DaTSCAN images.

Results

Subject Demographics:

Characteristics of the subjects are summarized in Table 18.

Table 18 Summary of Subject Demographics – Safety Population

			True Clinical Diagnosis at 24 Months (ITD)		
		Overall	PS (SDD)	Non-PS (No SDD)	No Diagnosis
Variable	Statistic	(N=120)	(N=48)	(N=30)	(N=42)
Gender					
Male	n (%)	60 (50%)	23 (48%)	18 (60%)	19 (45%)
Female	n (%)	60 (50%)	25 (52%)	12 (40%)	23 (55%)
Race					
Black	n (%)	1 (1%)	0 (0%)	0 (0%)	1 (2%)
Caucasian	n (%)	118 (98%)	47 (98%)	30 (100%)	41 (98%)
Asian	n (%)	1 (1%)	1 (2%)	0 (0%)	0 (0%)
Age (yr)	n	120	48	30	42
	Mean (SD)	65.1 (11.18)	64.3 (11.01)	64.0 (13.60)	66.7 (9.42)
	Min, Max	25, 84	35, 81	25, 84	40, 79
	Median	68.0	66.5	67.5	70.0
Height (cm)	n	118	47	29	42
	Mean (SD)	164.9 (8.95)	165.4 (7.67)	165.1 (9.53)	164.1 (9.99)
	Min, Max	145, 187	151, 185	146, 183	145, 187
	Median	164.5	165.0	165.0	162.5
Weight (kg)	n	118	47	29	42
	Mean (SD)	71.71 (14.742)	71.06 (14.315)	74.40 (14.809)	70.57 (15.283)
	Min, Max	37.0, 115.0	45.0, 106.0	37.0, 114.0	38.0, 115.0
	Median	71.25	72.00	77.00	70.00
BMI (kg/m^2)	n	118	47	29	42
	Mean (SD)	26.29 (4.712)	25.88 (4.438)	27.19 (4.819)	26.14 (4.960)
	Min, Max	14.3, 45.7	18.0, 35.4	15.4, 45.7	14.3, 38.5
	Median	25.93	25.95	26.93	25.40

N = total number of subjects; n = number of subjects with the respective demographic information; SD = standard deviation; PS = parkinsonian syndrome; BMI = body mass index; SDD = Striatal Dopaminergic Deficit.
Percentages are based on column totals.

Efficacy:

The information provided by DaTSCAN images had a major impact on subject diagnosis: 52% (61/118) of subjects' diagnoses changed following DaTSCAN SPECT imaging. The information from DaTSCAN images also led to a substantial reduction in uncertainty about whether or not the patient had PS. As expected, when there was a change in the confidence that the patient had PS, in approximately 80% of cases it was based on a DaTSCAN

assessment, and it was often associated with a change in planned management. Eighty-five (85) subjects (72%) had at least 1 change made in their management plan based on the DaTSCAN results. Changes included initiating a new therapy (41 subjects, 35%), changing the subject's follow-up (25 subjects, 21%), withdrawing therapy (18 subjects, 15%), and avoiding previously planned tests (28 subjects, 24%) [Catafau et al. 2004].

6.5 Efficacy Conclusions

It has been established for nearly 50 years that certain parkinsonian movement disorders involve extensive loss (50-60% loss) of nigrostriatal neurons prior to symptom onset, and it has more recently been found that DLB involves the loss of at least 30% of nigrostriatal neurons. Since ioflupane (the active component of DaTSCAN) binds to the DaT protein on these neurons, loss of these neurons could be predicted to result in the readily seen reductions of signal intensity in DaTSCAN images.

The clinical development program bore out these predictions, with high sensitivity and specificity (both approximately 90%) for the detection of an SDD, using expert clinical diagnosis as the SOT.

The clinical development program provides substantial evidence that visual assessment of DaTSCAN images provides high levels of sensitivity and specificity in detecting an SDD.

More recently, data from the Walker study have provided autopsy confirmation of DaTSCAN's ability to detect an SDD, using the most robust and objective SOT possible.

GE Healthcare believes that the preponderance of the evidence supports DaTSCAN's approval in the United States.

6.6 DaTSCAN Safety

6.6.1 Nonclinical safety assessment

The nonclinical safety assessment of DaTSCAN, including those studies forming the basis for approval of the product in Europe, has involved cardiovascular and CNS pharmacology (rats and dogs), single-dose toxicity (rats, rabbits, dogs, cynomolgus monkeys), repeated-dose toxicity (rats, rabbits and dogs), *in vitro* and *in vivo* genotoxicity studies. Deaths occurred in rats at doses equivalent to 320,000 times the maximum human dose (MHD) but not at 240,000 times the MHD. Deaths occurred in rabbits at MHD multiples of 135,000 but not 81,000. There were no deaths in dogs or cynomolgus monkeys injected with 30,000 and 5,500 times MHD respectively. Some pharmacological effects in rats such as hyperactivity and stereotypic behavior were noted at high doses: greater than 1,500 times the MHD. No effects on the electrocardiogram of conscious dogs were elicited at doses equivalent to 9,000 times the MHD. There was no evidence of genotoxicity.

6.6.2 Safety Assessment during Clinical Development

6.6.2.1 Drug Product Safety

The efficacy and safety data reported during clinical development present a very favorable risk/benefit picture for DaTSCAN. Data from all the clinical studies reveal a consistently benign safety profile for DaTSCAN with relatively few adverse events (AEs) and no serious AEs (SAEs) that were considered related to DaTSCAN administration.

In the 8 clinical studies completed in GE Healthcare's clinical development program, [^{123}I]ioflupane was administered intravenously to 972 subjects (907 patients and 65 healthy volunteers). All studies collected information on AEs, and most collected data on laboratory parameters (serum biochemistry, hematology and urinalysis), vital signs and Electrocardiograms (ECG). A comparable dose was used in all studies (3 to 5 mCi (111 to 185 MBq) of [^{123}I]ioflupane).

As expected, based on the very small mass dose of [^{123}I]ioflupane used in imaging (a maximum of 0.325 microgram), review of data on non-serious AEs, vital signs, laboratory parameters, and ECG found no safety issues.

Including an ongoing phase 4 clinical study (PDT409), the total number of subjects dosed with DaTSCAN as of December 31, 2008 in GE Healthcare clinical studies is therefore estimated to be 1,072 subjects: 1,007 patients and 65 healthy volunteers.

The imaging dose of ioflupane is too small for any abuse potential; DaT receptor occupancy is less than 1%, whereas at least 50% occupancy is needed for pharmacologic effects. In addition, distribution of DaTSCAN is strictly controlled owing to its radioactive nature and is provided only upon presentation of a valid prescription.

(a) Adverse Events

Table 19 presents a summary of AEs reported in the 8 studies. Overall, 588 AEs were reported, and of these, 73 (12%) were considered by the investigator to be at least possibly related to administration of DaTSCAN. A total of 231 (25%) subjects experienced at least 1 AE, and 39 (4%) subjects experienced an AE that was considered by the investigator to be at least possibly related to administration of DaTSCAN. However, the sponsor's analysis of common AEs with regard to causality suggests that none were related to DaTSCAN. Ten (1%) subjects experienced an AE that led to discontinuation from the study, but no subject experienced a DaTSCAN-related AE that led to discontinuation from the study. Thirty six subjects (4%) experienced at least 1 SAE, but no SAE was considered by the investigator to be related to DaTSCAN. Five subjects (<1%) experienced an SAE that led to death, but no fatality was considered related to DaTSCAN. There were no cocaine-like AEs reported.

Table 19 Adverse Event Summary (Safety Population)

	Overall N = 942 n (%)	Possibly DaTSCAN Related[1] n (%)
Number of AEs	588	73
Subjects with at least one AE	231 (25)	39 (4)
Subjects with at least one AE leading to discontinuation from the study	10 (1)	0 (0)
Subjects with at least one serious AE	36 (4)	0 (0)
Subjects with at least one AE leading to death	5 (<1)	0 (0)

N = Number of subjects dosed (used as the denominator for all percentages); n = number of subjects in each subgroup; AE = adverse event.
[1] At least possibly related to DaTSCAN according to the investigator.

Table 20 presents a summary of AEs reported by at least 2% of subjects. Events are presented by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC) by total and by maximum intensity. The most common SOC was nervous system disorders (85 subjects, 9%), followed by musculoskeletal and connective tissue disorders and gastrointestinal disorders (51 subjects each, 5%), infections and infestations (50 subjects, 5%), general disorders and administration site conditions (41 subjects, 4%), and vascular disorders (29 subjects, 3%). In each of the remaining SOCs the percentage of subjects with AEs was ≤ 2%.

Of the 231 subjects who experienced at least 1 AE, 110 (12%), 85 (9%), and 32 (3%) subjects had an AE with a maximum intensity of mild, moderate, and severe or incapacitating, respectively. For 4 (<1%) subjects the intensity of the AE was not reported. The SOC with the most severe or incapacitating AEs was injury, poisoning and procedural complications (7 subjects, <1%), followed by nervous system disorders (6 subjects, <1%). The following severe or incapacitating AEs occurred in more than 1 subject: fall and femoral neck fracture (3 subjects each, <1%); and abdominal pain, pneumonia, and joint dislocation (2 subjects each, <1%). All other severe or incapacitating AEs occurred in only 1 subject each.

Table 20 Adverse Event Reported by ≥2% of Subjects by System Organ Class, Preferred Term, and Intensity (Safety Population)

		Maximum Intensity			
System Organ Class Preferred Term	**Total N = 942 n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe/ Incapacitating n (%)**	**Missing n (%)**
Number of subjects with at least one AE	**231 (25)**	**110 (12)**	**85 (9)**	**32 (3)**	**4 (<1)**
Gastrointestinal disorders	**51 (5)**	**28 (3)**	**20 (2)**	**3 (<1)**	**0 (0)**
Nausea	20 (2)	14 (1)	6 (<1)	0 (0)	0 (0)
General disorders and administration site conditions	**41 (4)**	**24 (3)**	**14 (1)**	**2 (<1)**	**1 (<1)**
Infections and infestations	**50 (5)**	**32 (3)**	**15 (2)**	**3 (<1)**	**0 (0)**
Nasopharyngitis	16 (2)	11 (1)	5 (<1)	0 (0)	0 (0)
Injury, poisoning and procedural complications	**21 (2)**	**6 (<1)**	**8 (<1)**	**7 (<1)**	**0 (0)**
Investigations	**16 (2)**	**13 (1)**	**1 (<1)**	**0 (0)**	**2 (<1)**
Musculoskeletal and connective tissue disorders	**51 (5)**	**27 (3)**	**21 (2)**	**3 (<1)**	**0 (0)**
Nervous system disorders	**85 (9)**	**47 (5)**	**31 (3)**	**6 (<1)**	**1 (<1)**
Dizziness	20 (2)	15 (2)	5 (<1)	0 (0)	0 (0)
Headache	41 (4)	22 (2)	18 (2)	1 (<1)	0 (0)
Psychiatric disorders	**16 (2)**	**10 (1)**	**5 (<1)**	**1 (<1)**	**0 (0)**
Respiratory, thoracic and mediastinal disorders	**22 (2)**	**13 (1)**	**8 (<1)**	**1 (<1)**	**0 (0)**
Vascular disorders	**29 (3)**	**22 (2)**	**7 (<1)**	**0 (0)**	**0 (0)**

N = Number of subjects dosed. Used as the denominator for all percentages. AE = adverse event. n = number of subjects in each category or subcategory. Subjects with more than one occurrence within a category are only counted once.

The most common AE ascribed to DaTSCAN by the investigator was headache (13 subjects, 1%), followed by nausea (8 subjects, <1%), and vertigo, dry mouth, hunger, dizziness, and formication (3 subjects each, <1%). Most of these AEs were mild.

(i) Deaths

Table 21 presents a listing of the 5 deaths: 4 in study PDT304 and 1 in study PDT301. The fatal events were bronchial carcinoma (subject 03004-001-0122), pneumonia (subject 03004-004-0400), femoral neck fracture, myocardial ischemia, and left ventricular failure (subject 03004-004-0401), sepsis (subject 03004-006-0612), and femoral neck fracture (subject 301-047-0001). None was considered related to DaTSCAN by the investigator or the sponsor.

Table 21 Listing of Subject Deaths - Safety Population

Subject Number (PDT…)	Verbatim Term/ System Organ Class/ Preferred Term[a]	Onset Date/ Time End Date/ Time (yyyy-mm-dd/ hh:mm)	Onset Time Since Dosing/ Duration (d h m)	Intensity/ Relationship	Outcome
03004-001-0122	Hospitalization due to bronchial carcinoma/ Neoplasms benign, malignant and unspecified (including cysts and polyps)/ Bronchial carcinoma	2003-01-04/ 2003-01-04	466d 0h 0m (0d 0h 0m)	Severe or incapacitating/ Not related	Fatal
03004-004-0400	Pneumonia/ Infections and infestations/ Pneumonia	2004-02-13/ 2004-04-19	899d 0h 0m (66d 0h 0m)	Severe or incapacitating/ Not related	Fatal
03004-004-0401	Fractured left femoral neck/ Injury, poisoning and procedural complications/ Femoral neck fracture	2002-04-04/ 2002-04-13/ 04:15	219d 0h 0m/ (9d 0h 0m)	Severe or incapacitating/ Not related	Fatal
	Ischaemic heart disease/ Cardiac disorders/ Myocardial ischaemia	2002-04-10 2002-04-13/ 04:15	225d 0h 0m/ (3d 0h 0m)	Severe or incapacitating/ Not related	Fatal
	Left ventricular failure/ Cardiac disorders/ Left ventricular failure	2002-04-09 2002-04-13/ 04:15	224d 0h 0m/ (4d 0h 0m)	Severe or incapacitating/ Not related	Fatal
03004-006-0612	Septicaemia/ Infections and infestations/Sepsis	NA 2003-04-03	NA (NA)	Severe or incapacitating/ Not related	Fatal
301-047-0001	Fractured neck of femur, right/ Injury, poisoning and procedural complications/ Femoral neck fracture	2005-03-20 2005-04-25	3d 0h 0m (36d 0h 0m)	Severe or incapacitating/ Not related	Fatal

d = day(s); h = hour(s); m = minute(s); NA = not available.
[a] Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0.

(ii) Other Serious Adverse Events

Table 22 presents a summary of SAEs by SOC and Preferred Term, overall and by maximum intensity. Of the 36 subjects who experienced at least 1 SAE, 4 (<1%), 7 (<1%), and 25 (3%) subjects had SAEs with a maximum intensity of mild, moderate, and severe or incapacitating, respectively.

The most common SOC for SAEs were injury, poisoning and procedural complications; neoplasms benign, malignant and unspecified (including cysts and polyps); surgical and medical procedures; and gastrointestinal disorders (6 subjects each, <1%); followed by cardiac disorders, general disorders and administration site conditions, and nervous system disorders (4 subjects each, <1%); infections and infestations; respiratory, thoracic and mediastinal disorders (3 subjects each, <1%); and eye disorders (2 subjects, <1%). The System Organ Classes of blood and lymphatic system disorders, hepatobiliary disorders, investigations, and vascular disorders each had a single subject (<1%) with an SAE.

The most common SAEs were chest pain and femoral neck fracture (3 subjects each, <1%), followed by abdominal pain, pneumonia, fall, and joint dislocation (2 subjects each, <1%). All other SAEs occurred in only a single subject each.

Table 22 Serious Adverse Event Subject Summary by System Organ Class, Preferred Term, and Intensity (Safety Population)

System Organ Class Preferred Term	Total N = 942 n (%)	Maximum Intensity Mild n (%)	Moderate n (%)	Severe/ Incapacitating n (%)	Missing n (%)
Number of subjects with at least one SAE	**36 (4)**	**4 (<1)**	**7 (<1)**	**25 (3)**	**0 (0)**
Blood and lymphatic system disorders	**1 (<1)**	**1 (<1)**	**0 (0)**	**0 (0)**	**0 (0)**
Anemia	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	**4 (<1)**	**0 (0)**	**2 (<1)**	**2 (<1)**	**0 (0)**
Arrhythmia	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Atrial flutter	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Left ventricular failure	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Myocardial infarction	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Myocardial ischemia	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Eye disorders	**2 (<1)**	**1 (<1)**	**0 (0)**	**1 (<1)**	**0 (0)**
Blindness	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Cataract	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	**6 (<1)**	**1 (<1)**	**2 (<1)**	**3 (<1)**	**0 (0)**
Abdominal distension	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Abdominal pain	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)
Diarrhea	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Ileus	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Inguinal hernia	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Pancreatitis	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Reflux oesophagitis	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Vomiting	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
General disorders and administration site conditions	**4 (<1)**	**0 (0)**	**2 (<1)**	**2 (<1)**	**0 (0)**
Chest pain	3 (<1)	0 (0)	2 (<1)	1 (<1)	0 (0)
Malaise	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Pyrexia	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Hepatobiliary disorders	**1 (<1)**	**0 (0)**	**0 (0)**	**1 (<1)**	**0 (0)**
Hepatic lesion	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Infections and infestations	**3 (<1)**	**0 (0)**	**0 (0)**	**3 (<1)**	**0 (0)**
Pneumonia	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)
Sepsis	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Injury, poisoning and procedural complications	**6 (<1)**	**0 (0)**	**0 (0)**	**6 (<1)**	**0 (0)**
Fall	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)
Femoral neck fracture	3 (<1)	0 (0)	0 (0)	3 (<1)	0 (0)
Head injury	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Joint dislocation	2 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)
Wrist fracture	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)

Table 22 Serious Adverse Event Subject Summary by System Organ Class, Preferred Term, and Intensity (Safety Population)

System Organ Class Preferred Term	Total N = 942 n (%)	Maximum Intensity Mild n (%)	Moderate n (%)	Severe/ Incapacitating n (%)	Missing n (%)
Investigations	**1 (<1)**	**1 (<1)**	**0 (0)**	**0 (0)**	**0 (0)**
Arteriogram coronary	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**6 (<1)**	**0 (0)**	**1 (<1)**	**5 (<1)**	**0 (0)**
Bronchial carcinoma	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Bronchial neoplasm	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Gastric cancer	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Meningioma	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Non-Hodgkin's lymphoma	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Prostate cancer	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Nervous system disorders	**4 (<1)**	**0 (0)**	**0 (0)**	**4 (<1)**	**0 (0)**
Cerebrovascular accident	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Dementia	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Epilepsy	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Parkinson's disease	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Respiratory, thoracic and mediastinal disorders	**3 (<1)**	**0 (0)**	**3 (<1)**	**0 (0)**	**0 (0)**
Dyspnoea	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Pleural effusion	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Pulmonary embolism	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Surgical and medical procedures	**6 (<1)**	**2 (<1)**	**0 (0)**	**4 (<1)**	**0 (0)**
Heart valve replacement	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Intervertebral disc operation	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Knee arthroplasty	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Removal of internal fixation	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Renal transplant	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Salivary gland operation	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Vascular disorders	**1 (<1)**	**0 (0)**	**1 (<1)**	**0 (0)**	**0 (0)**
Varicose vein	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)

N = Number of subjects dosed. Used as the denominator for all percentages. SAE = serious adverse event; n = number of subjects in each category or subcategory.
Subjects with more than one occurrence within a category are only counted once.

(iii) Other Significant Adverse Events

Ten subjects (1%), all enrolled in the PDT304 study, had at least 1 AE that led to discontinuation from the study. The PDT304 study is the only study in which a post-injection AE could lead to a decision to discontinue additional administration of DaTSCAN. None of the AEs that led to discontinuation from the study were considered related to DaTSCAN.

In 4 of the 10 subjects the event or events were severe or incapacitating in intensity and had a fatal outcome. These are discussed above under Deaths. Other non-fatal events that led to discontinuation from the study were bronchial neoplasm, cerebrovascular accident, non-Hodgkin's lymphoma, pancreatitis, arthralgia, and renal transplant.

(iv) Adverse Events in Population Subgroups

Age

AEs were more frequent in subjects aged less than 65 (28% vs. 22%) and in subjects aged less than 75 (27% vs. 17%), but analysis of the event types did not reveal clinically significant differences.

Gender

More women than men reported AEs (27% vs. 23%), but examination of the event types did not reveal clinically significant differences.

Race

Because the overwhelming majority of subjects were Caucasian (99%), the profile of AEs by race is essentially the same as the profile for the overall Safety Population.

Renal Disease

Formal studies have not been carried out in subjects with significant renal impairment.

Hepatic Disease

Formal studies have not been carried out in subjects with significant hepatic impairment.

(b) Laboratory Data

There were no clinically significant mean changes from baseline for any serum biochemistry or hematology laboratory test. Urinalysis findings were unremarkable.

Laboratory range shift analysis showed that in general, shifts were between adjacent regions of the reference range and increases were generally matched by decreases, suggesting the changes were random (inconsistent with a drug effect). A notable exception was creatine kinase-MB fraction, which had a large proportion (28%) of shifts from high at baseline to normal post-injection. However, these changes were not in the direction of clinical concern.

(c) Vital Signs

There were no clinically significant mean changes from baseline for any vital sign (systolic and diastolic blood pressure, and pulse rate). In general, shifts between reference range regions were between adjacent regions and increases were generally matched by decreases, suggesting the changes were random (inconsistent with a drug effect).

(d) ECGs

There were no clinically significant changes from baseline in ECG data. In general, shifts were between adjacent regions of the reference range and increases were generally matched by decreases, suggesting the changes were random (inconsistent with a drug effect). There were no trends considered to be of clinical significance.

6.6.2.2 Radiation Safety

DaTSCAN contains the radioactive drug substance [^{123}I]ioflupane. The risks associated with nuclear medicine imaging procedures are well understood and accepted.

The sum of risk-weighted organ absorbed radiation doses is expressed in units of sieverts (Sv) and is known as the "effective dose". It is used as a measure of radiation risk.

The maximum recommended radioactivity dose for DaTSCAN is 5 mCi (185 MBq), which falls within the range of doses for other commercially available ^{123}I-labeled products in the USA: for example, the recommended adult dose for AdreView™ (iobenguane sulfate I 123) is 10 mCi (370 MBq). The absorbed radiation dose following such an injection of DaTSCAN is equivalent to a whole body effective dose of 4 to 6 millisievert (mSv).

To put this figure into perspective, the dose to the population due to natural background radiation in the USA is 3 to 4 mSv/year from terrestrial and cosmic radiation. It may be twice or three times this value in locations of high natural background or at altitude such as Denver, Colorado. The Nuclear Regulatory Commission has set a 5 mSv dose limit for members of the public exposed to patients administered radioactive materials. This dose of 5 mSv is also considered by the Nuclear Regulatory Commission to be an acceptable dose to the fetus of a pregnant radiation worker.

DaTSCAN is therefore considered safe from a radiation safety perspective.

6.6.3 Post-Marketing Safety

DaTSCAN is currently approved for marketing in 32 countries. DaTSCAN is manufactured and shipped to imaging centers and is used within a short time after manufacture. Patient exposure to DaTSCAN has therefore been estimated from the number of vials shipped by the manufacturing site. As of 17 June 2009, over 216,000 patients have been safely exposed to the product from clinical studies and the marketplace.

Hypersensitivity reactions have been reported during post-marketing use of DaTSCAN, though not in the clinical studies. Therefore, before administration, the patient should be questioned for a history of prior reactions to DaTSCAN. If the patient is known or strongly suspected to have hypersensitivity to DaTSCAN, the decision to administer DaTSCAN should be based upon an assessment of the expected benefits compared to the potential hypersensitivity risks. Injection site pain (following injection into small veins) has also been reported during the post marketing use of DaTSCAN.

As of 27 July 2007, 5 cases of severe pain on injection, 4 from the same hospital, had been received. The injections were apparently performed in a small vein on the back of the hand and this route may be a causal factor in the production of pain. The European labeling was amended to include injection site pain as an uncommon side effect.

One report of a serious adverse drug reaction after the administration of DaTSCAN™ has been received. The patient was a 76-year-old man with a history of stroke 12 years prior. He was administered 180 MBq (4.9 mCi) DaTSCAN intravenously for diagnosis of PS. Three and one-half hours after the administration the patient had an epileptic seizure. As the patient had abdominal discomfort for a few days he was examined, and cholecystitis and hyponatremia were diagnosed. After consultation with the neurologist the epileptic seizure was attributed to hyponatremia. The patient was treated with clonazepam and recovered after 30 minutes.

Three spontaneous case reports from healthcare professionals comprising 4 non-serious unlisted reactions (epistaxis, syncope vasovagal, hypersensitivity, and sense of oppression) and 1 non-serious listed reaction (headache) were received during the most recent reporting period.

No other reports have been received, either from the spontaneous reporting system, or from clinical studies, literature, or regulatory authorities.

No significant new information has been received regarding drug interactions, overdose, drug abuse or misuse, positive or negative experiences during pregnancy or lactation, experience in special patient groups (e.g., children, elderly, organ impaired), effects of long-term treatment or on increased frequency of side effects.

No application for Marketing Authorization for DaTSCAN has been declined by any National Regulatory Authority. There have been no deferrals or withdrawals. There have been no product recalls or restrictions on distribution. There have been no changes in target population or indication taken for safety reasons. There have been no curtailments of clinical study programs for safety reasons. No changes in formulation have been made to the product.

6.6.4 Safety Conclusion

DaTSCAN is a single-dose, diagnostic radiopharmaceutical given in sub-microgram doses; it can be concluded from both clinical study and routine use over 9 years that it is a safe product to administer.

7 SUMMARY

DaTSCAN is an effective and safe imaging modality to detect SDDs. Data from clinical studies demonstrates the usefulness of DaTSCAN as an adjunct to clinical diagnosis for both PS and dementia to enable the differentiation of PS from benign movement disorders such as ET and also the differentiation of DLB from AD.

In the two GE-sponsored studies in subjects with PS, DaTSCAN images were very effective in detecting or ruling out an SDD: one study enrolled subjects with definite PS and the other enrolled subjects with early or equivocal PS.

The GE-sponsored study in subjects with dementia, where the clinical question was to differentiate DLB from AD and vascular dementia, also showed DaTSCAN images to be highly effective in detecting and/or excluding an SDD.

Results to date from the ongoing Walker autopsy study provide autopsy confirmation of the ability of DaTSCAN images to detect and/or exclude an SDD in both dementia and PS subjects. This study provides definitive confirmation of DaTSCAN as an effective imaging tool to detect an SDD in accordance with the detection claim that is proposed.

The clinical studies reveal a consistently benign safety profile for DaTSCAN, with no concerns arising from ECGs, clinical labs, or vital signs, very few AEs and no SAEs that were considered related to DaTSCAN administration. This benign safety profile is supported by the post-marketing data.

By providing the clinician with an objective means to detect or exclude an SDD, DaTSCAN SPECT imaging will assist physicians in reaching an early and accurate diagnosis in patients with clinically uncertain signs and symptoms of dementia or movement disorder, and enable the prompt provision of appropriate therapy and minimize the possibility of a patient receiving unneeded or even deleterious treatment.

8 BENEFIT/RISK IN MOVEMENT DISORDERS AND DEMENTIA

8.1 DaTSCAN: Clinical Utility of DaT Imaging

A number of studies noted below have demonstrated that the assessment of patient dopaminergic status through [^{123}I]ioflupane imaging can be clinically useful by contributing to the differential diagnosis or exclusion of conditions; increasing confidence in diagnosis; allowing monitoring of disease progression; and supporting management decisions such as the appropriate withdrawal or initiation of dopaminergic medications.

8.1.1 Benefit in Movement Disorders

Differentiating ET and dystonic tremors from PD is important because of the difference in prognosis and therapy. The diagnosis of PD is frequently delayed for several years following the onset of symptoms because early symptoms and signs are subtle and relatively non-specific [Lees et al. 2009].

Though movement disorder experts are better than non-specialists at differentiating PD from other movement disorders such as ET [Kis et al. 2002, Jennings et al. 2004, Hughes et al. 2002], clinicopathologic autopsy studies demonstrate that diagnostic errors are not uncommon [Ward and Gibb 1990; Hughes et al. 1992; Litvan et al. 1998; Hughes et al. 2001]. It is not unusual for patients to be erroneously diagnosed with PD and to receive inappropriate therapy, possibly for years, as a result [Hensman and Bain 2006; Hagenah et al. 1999; Marshall et al. 2006b].

In the two GE-sponsored studies in subjects with PS, DaTSCAN images were very effective in detecting or ruling out an SDD: one study (DP008-003) enrolled subjects with definite PS and the other (PDT304) enrolled subjects with signs of early PS.

In addition to studies in the clinical program outlined previously, a number of independent studies reported in the literature support the use of DaTSCAN as an adjunct to diagnosis in patients with movement disorders. In a study of 72 patients with a diagnosis of suspected PS by a movement disorder specialist, DAT was reduced in 57/61 PS patients, whereas all 11 ET patients had normal DaTSCAN images [Plotkin et al. 2005]. In another study, 33 patients with an inconclusive assessment of PS by a movement disorder specialist (patients with a clear diagnosis were excluded) underwent DaTSCAN imaging. In nine of the patients, evidence of an SDD was found scintigraphically and in all these cases, PD was confirmed by clinical follow-up. In the other 24 subjects no SDD was seen with DaTSCAN and subsequent follow-up for at least 2 years excluded the subsequent development of PD [Booij et al. 2001].

Marshall et al. [2006b] were able to successfully withdraw anti-Parkinson medication in 11 patients after revision of diagnosis following normal DaTSCAN. Marshall and colleagues also

reported withdrawing anti-Parkinson medication in 27 subjects with normal DaTSCAN images, with no deterioration in 25 [Marshall et al. 2006a].

The acceptance of DaTSCAN for assessing patients with suspected movement disorders is reflected by the support for its use in evidence based consensus guidelines. Notably, the United Kingdom National Institute for Clinical Excellence (NICE) guidelines on Parkinson's disease [Royal College of Physicians, 2006] state:

> "The diagnosis of PD remains clinical. ^{123}I-FP-CIT SPECT may be of additional help in a small proportion of clinically uncertain cases. The diagnostic error rate on presentation may be as high as 10% in expert hands, which may lead to inappropriate therapy and distress following revision of the diagnosis."

In conclusion DaTSCAN enables the earlier and more accurate diagnosis of movement disorders by providing an objective method to identify SDDs and hence differentiate between PD and other more benign movement disorders.

8.1.2 Benefit in Dementia

Up to 30% of dementia patients have DLB. The diagnosis or exclusion of DLB is especially important because patients with DLB have a tendency to experience vivid hallucinations and other psychotic symptoms, for which they may be administered neuroleptic drugs. However, DLB patients can be very sensitive to neuroleptic drugs and experience serious side effects which may be fatal. As a result, neuroleptic drugs are contraindicated in DLB patients [McKeith et al. 2005; Mosimann and McKeith 2003; Aarsland et al. 2005].

The GE-sponsored study (PDT301) in subjects with dementia, where the clinical question was to differentiate DLB from AD and vascular dementia, showed DaTSCAN images to be highly effective in detecting and/or excluding an SDD.

Walker and colleagues have investigated the utility of DaTSCAN in contributing to the diagnosis or exclusion of DLB, using eventual autopsy as the reference standard. Results to date in 27 autopsied patients indicate that visually interpreted DaTSCAN images have high sensitivity (84.6%) and specificity (85.7%), which was a substantial improvement over the clinical assessment at baseline in specificity (84.6% and 50.0%).

DaTSCAN has been incorporated into several evidence-based consensus guidelines on cognitive disorders. The International Consensus Criteria on diagnosis of DLB [McKeith et al. 2005] state:

> "Suggestive features: If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.
>
> - REM sleep behavior disorder

- Severe neuroleptic sensitivity
- Low DaT uptake in basal ganglia demonstrated by SPECT or positron emission tomography (PET) imaging"

The United Kingdom NICE guidelines on dementia [Royal College of Psychiatrists, 2007] state that:

> "Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT should be used to help establish the diagnosis in those with suspected DLB if the diagnosis is in doubt."

In summary DaTSCAN is an effective diagnostic agent in dementia patients that is helpful in the differentiation of AD and DLB.

8.1.3 Risk/Benefit in Movement Disorders and Dementia

The absence of significant safety issues with DaTSCAN based on the experience in clinical trials in both movement disorder patients and dementia patients and the post-marketing experience resulting from 9 years experience in Europe in conjunction with the consistent evidence of efficacy provides a very positive risk/benefit profile. The availability of DaTSCAN in the United States will enhance the clinical management of patients with both movement disorders and dementia, particularly those with equivocal diagnoses.

9 OVERALL CONCLUSIONS

DaTSCAN is an imaging tool that allows physicians to easily and visually determine the presence or absence of an SDD. A clinicopathologic autopsy study has validated the efficacy of DaTSCAN in the detection of a SDD. Knowledge of SDD has clinical utility and could help physicians manage and treat patients more appropriately when combined with clinical information.

DaTSCAN images show high contrast between the striata and other brain regions, allowing images to be interpreted by simple visual inspection. Normal and abnormal images are easily to differentiate. DaTSCAN images provide an objective record of whether or not a patient has an SDD. DaTSCAN is thus an objective adjunct to diagnostic workup.

The safety and efficacy of DaTSCAN as a marker of nigrostriatal dopaminergic status have been demonstrated in clinical trials with over 1,000 total subjects recruited. DaTSCAN has been used routinely for over 9 years in 32 countries. It is estimated that over 216,000 doses have been dispensed.

DaTSCAN would benefit patients and physicians in the USA by helping to improve the differential diagnosis of both movement disorders and dementias.

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11 APPENDICES

11.1 DaTSCAN Image Interpretation

DaTSCAN Image Interpretation

DaTSCAN images that have been acquired correctly (i.e., correct amount of administered DaTSCAN, correct time to start imaging post-injection, and correct total counts) can be interpreted visually. Reconstructed pixel size should be between 3.5 and 4.5 mm with slices 1 pixel thick. Optimum presentation of the reconstructed images for visual interpretation is transaxial slices parallel to the anterior commissure-posterior commissure line. Determination of whether an image is normal (consistent with no loss of functional nigrostriatal dopaminergic neurons) or abnormal (consistent with a loss of functional nigrostriatal dopaminergic neurons) is made by assessing the extent (as indicated by shape) and intensity of striatal activity.

Normal Uptake:

In transaxial images, normal uptake is characterized by two symmetric comma- or crescent-shaped focal regions of activity mirrored about the median plane. There is good contrast relative to surrounding brain tissue (Figure 4).

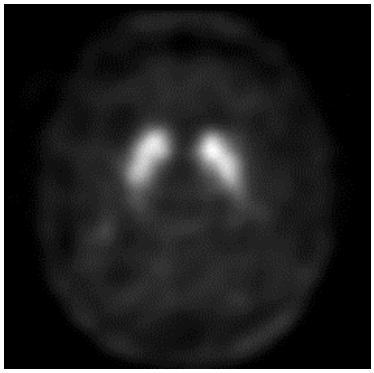

Figure 4 Normal Uptake

Abnormal Uptake:

With disorders involving a loss of functional nigrostriatal dopaminergic neurons, DaTSCAN uptake is almost always reduced first in the posterior putamen, often asymmetrically. Abnormal DaTSCAN images fall into one of the following 3 categories (all are considered abnormal and do not necessarily reflect the severity of symptoms):

- Uptake is asymmetric with activity in the putamen of one hemisphere absent or greatly reduced with respect to the other. Uptake is still visible in the caudate nuclei of both hemispheres resulting in a comma or crescent shape in one and a circular or oval focus in the other. There is often reduced contrast between at least one striatum and surrounding tissues (Figure 5).

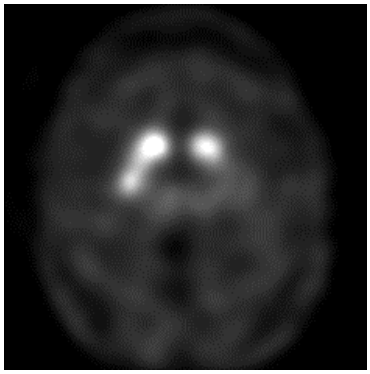

Figure 5 Abnormal Uptake Type 1

- Uptake can be virtually absent in the putamen of both hemispheres and confined to the caudate nuclei. Uptake is relatively symmetric and forms two roughly circular or oval foci. Contrast of one or both is generally reduced (Figure 6).

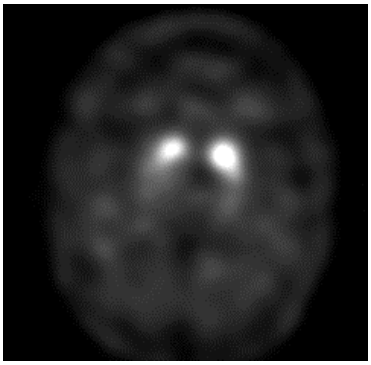

Figure 6 Abnormal Uptake Type 2

- Uptake is absent in the putamen of both hemispheres and will be greatly reduced in one or both caudate nuclei as well. Contrast of the striata with respect to the background is significantly reduced (Figure 7).

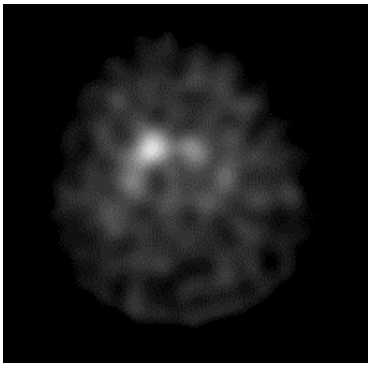

Figure 7 Abnormal Uptake Type 3